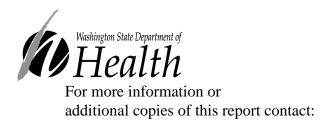# Evaluation of Evidence Related to the Development of a Tolerable Daily Intake for Methylmercury

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Washington State Department of
Health

Office of Environmental Health Assessment Services

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Acknowledgement

Contents

Executive Summary

Human exposure to environmental concentrations of methylmercury has made this a chemical of global concern. Exposure through diet has resulted in increased body burdens of methylmercury in human populations. Catastrophic community exposures have resulted in severe toxic and teratogenic effects. Methylmercury can readily cross the placental barrier, following adult exposure, resulting in prenatal exposures that can lead to developmental effects, including central nervous system damage, which can produce neurotoxic effects in children. Available data indicate that the population of greatest concern consists of women of child bearing age and infants. There is no longer doubt about the ability of methylmercury to produce deleterious effects in animals and humans. However, determining the exposure level that will not cause concern for offspring of mothers exposed for a finite period of time is problematic.

Two major scientific studies that have provided great insight into the possible effects from exposure to methylmercury were recently conducted in the Seychelles Islands and in the Faroe Islands. The Seychelles Islands study investigated the effects of prenatal exposure to methylmercury through maternal fish consumption by testing for fetal neurodevelopmental effects at several timepoints during infancy and childhood. The main cohort consisted of 740 mother-infant pairs with no definite adverse neurodevelopmental effects observed in the offspring from low-level methylmercury exposure. The Faroe Islands cohort was generated from 1022 consecutive singleton births during 1986 and 1987. The cohort of children born to mothers with an average mercury hair level of 4.3 ppm (n = 917) underwent neurobehavioral examination at age seven. Although no mercury-related abnormalities were observed based on clinical examinations, mercury-related neuropsychological dysfunctions in language, attention and memory were observed. Whether these low-level methylmercury exposures will produce delayed effects in these populations or if the effects observed in the Faroe Islands cohort are chronic or transient, remains to be determined.

In the state of Washington, data exist showing that individuals consume fish contaminated with methylmercury. To determine if Washington residents are consuming contaminated fish in quantities that could possibly result in deleterious outcomes, the Department of Health has determined a tolerable daily intake (TDI) for methylmercury that is unlikely to result in adverse health effects. This intake level, which is provided as a range, was based on scientific studies investigating sensitive endpoints in children of mothers who consume fish over prolonged periods of time. The sensitive endpoints are impaired neurological development and, long-term and/or delayed sequelae in children exposed prenatally to methylmercury. Evidence related to the development of this TDI and the uncertainties associated with its derivation, including toxicodynamic variations and pharmacokinetic variability, are discussed. Based on our review of available data, an intake of methylmercury in the range of 0.035 to 0.08 µg/kg/day constitutes a TDI that is deemed to not result in adverse health effects.

Intake values for methylmercury established by other individuals, groups or agencies are shown in the table below:

Individuals/Group/Agency (Reference)	Primary Studies Required to Establish Intake Level	Intake Level(s)
Stern (Stern, 1993)	Weight of evidence; animal and human data	0.07 µg/kg/day
Burbacher (Zelikoff, 1995)	Animal data and other	0.01 µg/kg/day
Gilbert and Grant-Webster (Gilbert and Grant-Webster, 1995)	Iraq episode data and other	0.025 – 0.06 µg/kg/day
Rice (Rice, 1996a)	Macaque monkey data	0.01 µg/kg/day
USEPA (USEPA, 1997)	Iraq episode data and other	0.1 µg/kg/day
ICF Kaiser (Clewell et al. 1998)	Seychelles Islands data and other	0.3 – 1.0 µg/kg/day
ATSDR (ATSDR, 1999)	Seychelles Islands data and other	0.3 µg/kg/day
Washington State Dept of Health	Faroe Islands data and other	0.035 – 0.08 µg/kg/day

Available fish consumption data for diverse populations within the state will be used with fish contaminant data to determine if specific segments of Washington State residents or populations within Washington State are possibly exceeding this TDI. This determination will allow the Department and Local Health Jurisdictions to develop intervention and education strategies to protect Washington State residents from overexposure to methylmercury.

Introduction

Environmental exposure of human populations around the world to methylmercury has made this a chemical of global concern. Exposure through diet has resulted in increased body burdens of methylmercury in human populations (ATSDR, 1997; USEPA, 1997). Catastrophic exposure by communities in Japan and Iraq has resulted in severe toxic and teratogenic effects (Harada, 1995). Laboratory studies in animals, both rodent and non-human primate, have indicated various reproductive, developmental and neurological effects from exposure (Khera, 1973; Chang et al., 1974; Sato and Ikuta, 1975; Bornhausen et al., 1980; Mohamed et al., 1987; Burbacher et al., 1988; Mitsumori et al., 1990). Methylmercury can readily cross the placental barrier following adult exposure, resulting in prenatal exposures that can lead to developmental effects, including central nervous system damage which can produce neurotoxic effects in children (ATSDR, 1997; USEPA, 1997). These effects on the developing nervous system are considered to be the most sensitive endpoint (ATSDR, 1997; USEPA, 1997). Observed effects from *in utero* exposure in poisoning episodes have included blindness, deafness, abnormal reflexes, impaired motor development, spasticity, seizures and deficiencies in memory, learning and psychological parameters (ATSDR, 1997). The available data clearly indicate that the population of greatest concern consists of women of child bearing age and infants. There is no longer doubt about the ability of methylmercury to produce deleterious effects in animals and humans. However, determining the exposure level that will not cause concern for offspring of mothers exposed for a finite period of time is problematic. This difficulty stems from the fact that while the developmental and neurotoxic effects of methylmercury at elevated levels of exposure have been well-studied, the effects from low levels of exposure and from *in utero* exposures associated with deleterious effects, are only now becoming understood.

Human Data

The first mass outbreak of poisoning from methylmercury occurred when heavily contaminated fish were consumed by individuals living in Minamata, Japan during the 1950s and 1960s (Harada, 1995). This incident was of great significance since it was the first evidence that methylmercury, discharged by a factory into Minamata Bay, was bioaccumulating and biomagnifying in locally caught fish. The outbreak in Japan indicated that the prenatal period was a very sensitive period for exposure to methylmercury since severely brain damaged infants were born to mothers who hardly showed ill effects (WHO, 1990). Laboratory animal experiments supported this conclusion by providing evidence that the developing brain was very sensitive to exposure (Burbacher et al.; 1990; Evans et al.; 1975; Rice; 1983; Willies et al., 1978).

The first quantitative dose-response relationship of methylmercury poisoning in humans addressing developmental effects was estimated from an incident that occurred in Iraq in the winter of 1971-1972. Imported seed grain contaminated with methylmercury fungicide was used to prepare homemade bread throughout rural areas of Iraq (Amin-Zaki et al., 1976, 1979, 1981; Bakir et al., 1973; Marsh et al., 1981,1987). The Iraqi outbreak was considered an acute exposure (duration of one month) that provided quantitative information on prenatal exposure to methylmercury. Mother-child pairs were studied to determine if the presence of

3

methylmercury in maternal hair was associated with developmental and neurological abnormalities in offspring. Through the use of a parametric threshold model, an apparent threshold for delayed walking was estimated to occur at mercury maternal hair concentrations ranging from 10 ppm to >100 ppm.

To test the findings obtained from the Iraqi experience, a prospective longitudinal study was designed that investigated a larger population that was chronically exposed to mercury through the most common route of methylmercury exposure, ingestion of contaminated fish. This study was conducted in the Seychelles Islands where consumption of fish (≈12 fish meals/week) is the sole source of methylmercury exposure (Davidson et al., 1995, 1998; Marsh et al., 1995a; Myers et al., 1995). As in Iraq, mercury levels in maternal hair were measured during pregnancy. In contrast to the Iraqi study, however, much more sophisticated methods of measurement were used for determining neurological developmental competency. Although levels of mercury in the hair of some mothers exceeded 10 ppm, intensive and repeated testing of children in this study found no evidence that prenatal methylmercury exposure is linked to adverse developmental effects. In fact, these children achieved some motor developmental markers sooner than children of western societies.

A study of a population that consumed methylmercury contaminated fish in New Zealand, investigated the effects on children from prenatal exposure to methylmercury (Kjellstrom et al., 1986, 1989). As with the Seychellois population study, this study relied on continuous scale evaluations of cognitive function and on evaluations of subclinical neurological developmental performance rather than gross neurological signs, as was the case in the Iraqi study. Results suggested developmental effects had occurred in children whose mothers had methylmercury hair levels of 6 ppm and above (Kjellstrom et al., 1986, 1989). A re-evaluation of these data using bench mark dose (BMD) modeling resulted in a statistical lower bound maternal hair mercury level, which can be used to determine acceptable human exposures, that ranges from 7.4 - 10 ppm (Crump et al., 1998).

Along with these four population groups (Japan, Iraq, New Zealand and the Seychelles Islands), other studies consisting of subject groups in locations such as Peru, Samoa, New Guinea, Canada, and the Amazon have also been completed or are ongoing (Kyle and Ghani 1982; Marsh et al. 1974, 1995b; McKeown-Eyssen and Reudy 1983a, 1983b; Turner et al. 1980; Wheatley and Paradis 1995, 1996; Wheatley et al. 1979, 1997; Lebel et al. 1996, 1997; Lodenius and Malm 1998). With the exception of the Amazon study, results failed to associate adverse effects with mercury exposure.

A large study consisting of more than 1000 mother-child pairs in the Faroe Islands is presently being conducted to examine developmental effects from exposure to methylmercury due to consumption of contaminated fish and pilot whale meat (Grandjean et al., 1992, 1994, 1995, 1997, 1998). Although only limited dose response data are available from this study, results from the extensive neurophysiological examinations suggest that *in utero* exposure affects brain function and that early dysfunction in children is detectable at exposure levels resulting in maternal hair mercury levels below 10 ppm.

Supporting Animal Data

Information has been obtained on the effects of methylmercury in rodents and non-human primates. Results of animal studies have demonstrated effects at high doses similar to high dose effects observed in humans. However, low dose effects from methylmercury exposure have not been characterized to the extent that allows for detailed comparison between animal models and humans.

The best available data from relatively low dosages come from two monkey cohorts exposed until age seven, one group exposed post-natally and the other pre- and post-natally (Rice, 1992, 1996). Exposed infants showed performance alteration from a fixed-interval operant learning task, suggesting changes in time perception. However, these same animals did not show learning impairments based on results from discrimination reversal tests. These developmental effects were observed at exposure levels of 10 and 25 μg/kg/day and represent the lowest non-acute exposure regiment administered to non-human primates (Rice, 1992, 1996a). Although, sensitivity to methylmercury- induced developmental neurotoxicity of monkeys and humans appears to be similar at elevated exposure levels, non-human primate data at the lower end of the dose-response curve will be required before we can effectively use this model, in the place of human data, to protect public health.

With the developing brain being very sensitive to methylmercury exposure, long-term and delayed effects have also been investigated in primates. Takahata and co-workers (1970) initially indicated that exposure to mercury resulted in the accumulation and possible persistence of mercury in the human brain. Methylmercury exposed monkeys have been shown to concentrate inorganic mercury in the pituitary and thalamus by demethylation of methylmercury in the brain (Vahter et al., 1994, 1995). Half-life values for mercury at these two brain sites indicate that inorganic mercury could remain in the brain for many years, possibly for a lifetime. Whether the high concentrations of inorganic mercury in the brain are of toxicological consequence remains to be determined. The inorganic mercury could be tightly bound to sulfhydryl groups and thereby not represent great concern or be in a chemical form capable of producing delayed or long-term effects. Experiments with primates in which exposure levels resulted in long-term and/or delayed sequelae in offspring have also been shown to produce developmental and neurological abnormalities (Burbacher et al., 1990; Rice, 1992, 1996a, 1996b; Rice and Gilbert, 1995). Before these types of data can be used for public health protection, further work is required to determine if there are effects associated with the long-term retention of inorganic mercury in the brain and if long-term or delayed sequelae occur at levels below those that result in impaired neurological development.

Studies using rats that were treated prenatally with methylmercury during days six through nine of gestation have attempted to elucidate low-level exposure effects based on results from tests measuring schedule-controlled operant behavior in offspring (Bornhausen et al., 1980; Musch et al., 1978). The progeny were required to respond a specified number of times within a fixed time interval, with results indicating no observable effects at 5 μg/kg/day, while the rats exposed to 10 μg/kg/day had reduced success rates in testing. Direct exposure data from

rodents, however, have severe limitations when attempting to draw similarities to humans since the ratios of mercury concentration in brain and blood of the rodents are significantly different from the ratio in humans. Thus, to use animal data, an understanding of methylmercury distribution and partitioning within each species will be required to delineate the importance of species differences such as the observed 100-fold difference in the brain-blood distribution ratios between species (Magos, 1987; Burbacher et al., 1990).

Comparison of Animal and Human Data

In an attempt to make sound comparisons between species, methylmercury dose-response relationships have been investigated that compare effects based on target-organ dose, which in this case is the brain. This approach avoids dealing with differences in tissue distribution between species, which has made exposure-based comparisons difficult. From available study results, qualitative and quantitative comparisons of neuropathological and neurobehavioral effects among humans, non-human primates and rodents have been made based on target-organ dose (Burbacher et al., 1990). In making the quantitative comparisons, studies were used in which: (1) brain/blood mercury ratios were known, (2) exposure scenarios were similar to those studies in which brain- mercury levels were known, and (3) brain dose could be estimated based on brain-blood distribution ratios. The latter studies were primarily those in which mercury-brain levels were not known, and where extrapolation based on exposure was not possible. Although difficulties can arise using brain-blood distribution ratios because they are derived from limited data, and because methylmercury concentrations vary across different brain regions within individuals, they do allow for comparisons across finite ranges of target-organ doses.

Qualitative neuropathological results associated with developmental effects indicate that there is excellent agreement in endpoints of toxicity between humans and non-human primates, with the exception that the cerebellum of non-human primates does not appear to be a major target of adult or prenatal methylmercury exposure (Garman et al., 1975; Hunter and Russel, 1954; Mottet et al., 1987; Takeuchi and Eto, 1972). Generally, there is a high degree of similarity in neuropathological endpoints from high dose methylmercury exposure across all species (Burbacher et al., 1990; Choi,et al., 1978). Effects include decreased brain size, loss of cells, and damage to cortex and basal ganglia (Burbacher et al., 1990). An endpoint that may be species related, is ectopic cells and disorganized lamination which have been observed in humans and primates; the only non-primate species in which this has been observed is guinea pigs (Burbacher et al., 1990; Inouye and Kajiwara, 1988). Neurobehavioral endpoints have been much more difficult to compare across species because differences in procedures used to determine effects from exposure have led to little agreement when addressing specific endpoints. Only when comparing broad categories in behavior can species similarities be made. Tests addressing neurodevelopmental endpoints, adapted from those done on human infants, such as object performance and visual recognition memory, will be of immense value in comparing species since they have been performed on non-human primates and now are being used in studies on populations exposed to methylmercury.

Quantitative neurological effects in humans and animals have been observed at target-organ levels of approximately 12 ppm (Choi,et al., 1978; Harada, 1977; Harada 1995; Inouye et al., 1985; Matsumoto et al., 1965; Mottet et al., 1987). Animals with similar brain mercury levels have shown effects such as increased activity, altered response to challenge from other compounds, and changes in ability to perform learning tasks (Inouye et al., 1985; Mottet et al., 1987). Clinical effects from the individuals exposed in Iraq have been suggested to occur at brain levels of 1ppm (Cox et al., 1989). Animals have shown changes in two-way avoidance tasks with mercury-brain levels below 4 ppm while tests using differential reinforcement of high rates have shown alterations at brain levels at and below 0.1 ppm (Burbacher et al., 1990). Exposure to methylmercury through contaminated fish in New Zealand suggests that maternal hair concentrations above 6 ppm, which corresponds to brain levels of 0.3 ppm, could induce effects (Kjellstrom et al., 1986). The Seychelles Islands study suggests that maternal hair of 10 ppm, corresponding to estimated brain levels in children of 0.5 ppm, are not associated with adverse developmental effects (Davidson et al., 1995; Davidson et al., 1998; Marsh et al., 1995a; Myers et al., 1995). Also, autopsy brain tissue from infants, in which levels of total mercury were all less than 0.3 ppm, were examined with no demonstrated evidence of toxicity being observed (Lapham et al., 1995). The estimated brain level, 0.5 ppm, in the Seychellois population may display some variability from other study results however, since the blood to hair distribution ratio in this study was 415 μg Hg/g hair/mg Hg/l blood whereas the global norm is considered to be 250. It must be noted, however, that this ratio was determined from samples obtained at parturition and so may not be directly comparable to the global norm. Finally, initial results from the Faroe Islands study suggests that levels of maternal hair below10 ppm may affect brain function (Grandjean et al. 1992, 1994, 1995, 1997, 1998). The average mercury level in maternal hair for this population was 4.3 ppm, and although only limited dose-response data are available, the data do suggest that effects in this population occur at exposure levels considered to not produce effects in the Seychellois population.

To determine exposure levels that are of health consequence, human studies use biomarker measurements such as mercury-brain, mercury-blood, mercury-cord blood and mercury-hair levels. Although difficulties can arise in using and comparing these exposure metrics, much insight can be gained if used for comparisons across finite ranges of doses. Brain-blood ratio for non-human primates has been calculated to be 2.6, while for humans it is 6.0 (Magos, 1987). Rats have been shown to have a brain-blood mercury ratio of 0.06 (Magos, 1987). Maternal hair mercury levels, which are most frequently used in human studies, are considered to be 250 times greater than maternal blood concentrations (units being μg Hg/g hair /mg Hg/l blood) on average (Inskip and Piotrowski, 1985). Although this value is commonly used, the study population in Peru had a hair-blood ratio of 190, and the reported value from the Seychelles Island population is 415 (Davidson et al., 1995; Marsh et al., 1995a, 1995b; Myers et al., 1995). Attempts to relate mercury intake levels to mercury-blood and mercury-hair concentrations in humans have also been made with a blood-intake ratio being approximately 70 (units being μg Hg/l /μg Hg/kg/day) and hair-intake ratio being approximately 18 (units being μg Hg/g /μg Hg/kg/day) (Lipfert et al., 1996). Uncertainties in these biomarker values can greatly alter expected exposure-effect relationships, however. As a result, it has been suggested that uncertainties dealing with exposure errors could be better controlled for if data for more than one exposure metric or biomarker were obtained (Lipfert et al., 1997).

Individual Variability

The uncertainty in exposure makes for difficulty in determining effect levels, and interindividual variability further complicates the issue. Hattis and Silver (1994) have suggested that if the uncertainties in individual exposure estimates could be measured or better defined, a much better approximation of the slopes of the underlying dose-response curve could be constructed. It has also been suggested that for women of age 18 – 40, interindividual variability, such as individual pharmicokinetic variability, could result in further restricting the daily methylmercury intake level considered to do no harm (Stern, 1997). Age and gender issues in animals have also been addressed as factors that can impact mercury elimination rates. There may be an age-dependent development that allows for more efficient elimination of methylmercury, thereby more rapidly decreasing the body burden (Nielson and Anderson, 1996). The possibility that various factors can play a significant role in determining the extent of toxicity from exposure suggests that these factors need to be considered and controlled for when studying populations exposed to methylmercury.

Establishing a Tolerable Daily Intake Level

Considerable effort has been put forth by various agencies, groups, and individuals to determine a mercury exposure level that would not result in adverse human health effects. Target-organ dose based dose-response relationships could be instrumental in determining the levels of *in utero* methylmercury exposure that lead to neurological effects in infants and children; however, available human and animal data do not presently allow for adequate relationships to be derived that can be used to protect public health. Conditions of acute methylmercury exposure have shown the fetus to be particularly sensitive to methylmercury with adverse effects on infant development being documented in the absence of maternal toxicity or clinical illness (ATSDR, 1997; USEPA, 1997). Stern (1993) considered the available human and animal study data addressing developmental endpoints and suggested that the weight of evidence indicated that the RfD should be 0.07 µg/kg/day. With the understanding that the fetus and infant are more sensitive to adverse effects from methylmercury exposure, Gilbert and Grant-Webster (1995) used the Iraq episode data, supported by data on neurobehavioral effects in animals, to develop a Reference Dose (RfD) range of 0.025 to 0.06 µg/kg/day. Zelikoff and co-authors (1995) considered various approaches for establishing an RfD based on prenatal methylmercury exposure effects in small mammals, nonhuman primates and humans. These approaches were provided since establishing an RfD based on adult clinical effects may not be appropriate for protecting the developing fetus. The lowest RfD, 0.01 µg/kg/day, was derived from effects seen in rats where abnormal performance was observed in behavior using a differential reinforcement of high rates paradigm. Rice (1996a) has suggested that RfDs derived from animals are in agreement with those obtained from human data. Macaque monkey data from two data sets using different exposure regimens, but identical daily dosages (50 µg/kg/day methylmercury) yielded an RfD of 0.05 µg/kg/day following the method used by USEPA (Gilbert et al., 1993; Rice, 1992). Monkeys dosed at 10 or 25 µg/kg/day *in utero* until age four showed developmental effects due to sensory-system impairment (Rice, 1992, 1996a). These data lead to an RfD of 0.01 µg/kg/day. The recently released Mercury Report to

Congress (1997) by the USEPA provided an RfD for methylmercury based on BMD modeling using the results from the study on Iraqi mother-child pairs. The Seychelles Islands study, the Faroe Islands study and other recent studies were not included in deriving this RfD, which is 0.1 µg/kg/day. ATSDR (1997) has used the median hair level of the entire Seychelles Islands study cohort, with uncertainty factors, to derive a Minimal Risk Level for methylmercury of 0.3 µg/kg/day. Clewell and co-workers (1998) have used the results from several child development tests obtained from the Seychelles study to derive a BMD in hair of 20 ppm methylmercury. This BMD along with daily ingestion rates allowed for the determination of RfDs that range from 0.3 to 1.0 µg/kg/day (median 0.54 µg/kg/day).

The most common route of exposure to methylmercury is through fish consumption with the exposure period of concern being long-term and with the sensitive endpoints being impaired neurological development and, long-term and/or delayed sequelae in children of exposed mothers. As a result, quality studies investigating sensitive endpoints in children of mothers consuming fish over prolonged periods of time are preferable to rodent and non-human primate data and to human data addressing endpoints where exposure was through another means or for shorter time periods. Presently the investigations completed or ongoing in New Zealand, the Seychelles Islands and the Faroe Islands clearly are quality studies of this type. These are prospective longitudinal studies of cohorts in which attempts were made to control for many of the factors that could influence child development, resulting in increased ability to detect neurological effects and delayed sequelae from methylmercury exposure. The cohort studied in the Seychelles was larger than that in New Zealand while the Faroe Islands study results have become available recently with further observations forthcoming. Clewell and co-workers (1998) and ATSDR (1997) have considered the available data and used the Seychelles data and corroborating evidence from the studies in New Zealand and Faroe Islands to derive RfDs. Quite contrary to this approach, the USEPA's Science Advisory Board has recommended that no changes to USEPA's Iraqi study-based RfD be made in the Mercury Report to Congress until further and more definitive data from the Seychelles Islands and Faroe Islands become available.

These discrepancies in approaches used to determine tolerable daily intake levels or reference doses, which include different approaches to address uncertainty, have occurred for many reasons dealing primarily with the limitations of the available data sets from the various studies. For example, the Iraqi population is considered not to be representative of a sensitive subpopulation within the perinatal group when compared to the populations from the Faroe Islands, the Seychelles Islands, and the Peruvian fishing villages (Cicmanec, 1996). With respect to the Seychelles Islands, the seafood contains essential nutrients, such as n-3 fatty acids, that could act as effect modifiers whereas in the Faroe Islands, these nutrients as well as PCBs could be effect modifiers. The presence of these nutrients in fish consumed by the Seychellois population cohort has resulted in the suggestion that the beneficial effects of fish consumption may outweigh any possible adverse effects from mercury exposure (Bolger, 1998). Although not observed in the Faroe Islands cohort, the Seychelles Islands cohort is achieving some developmental milestones more quickly than children in western cultures (Davidson et al., 1998). However, the correlation coefficients values for the regression analyses of the full model for many of the endpoints studied in the Seychellois population were low indicating that

it was not possible to include all consequential factors (i.e. genetic variability or predisposition) that predict infant development in the model and, as a result, the tests may lack the sensitivity to detect subtle developmental effects (Davidson et al., 1995, 1998). The authors suggest that their data set of individuals exposed at levels where effects appear may be too small to have a great deal of confidence in the results (Davidson et al., 1995, 1998). Also, there are potentially many population-specific considerations and confounding factors which make the basis for the rapid achievement of these developmental milestones unclear. It has been suggested that the Faroe Islands cohort may provide better data since that population is exposed to PCBs along with mercury, as is the case for many in the US (Mahaffey, 1998). Also, the Seychellois population is exposed chronically to lower contaminant levels whereas in the US, populations consume fish less frequently, but with higher contaminant levels (Mahaffey, 1998). However, the Seychellois population may represent a cohort that better approximates fish consumers in the US than does the cohort in the Faroe Islands since US populations do not consume pilot whale (Bolger, 1998).

Based on the present results, various individuals and organizations have taken different approaches to deriving safe or tolerable consumption levels for human populations. The USEPA levels continue to be based on data from Iraq, with further consideration awaiting more conclusive results from the Seychelles Islands and Faroe Islands. Others have decided, for example, that the current data from the Seychelles Islands can be used at this time. Since public health protection is typically required without complete scientific clarity, it is clear that the process of establishing tolerable consumption levels will be a continuous one, responding to new findings as they become available. Whereas present available human and animal data are sufficient to attempt public health protection, great strides in determining these protective levels will be made as the *in utero* exposure knowledge base is further delineated. An exposure level that will render a platform from which to protect public health, however, can not be provided without giving foremost consideration to those studies suggesting that effects may occur at low levels of exposure. Preferentially relying on data indicating that no observable deleterious effects arise from chronic low level mercury intake, as is the case with the Seychellois population data, would undermine public health ideals which demand that observations indicating causal effects from exposure require consideration when protecting public health. As a result, the findings from the New Zealand study and the available findings from the Faroe Islands study must be considered even though significant work from the Seychelles Islands may provide a contrasting view.

Despite their respective shortcomings (i.e. lack of dietary information for cohorts in the Faroe Islands and Seychelles Islands, concomitant PCB exposure in the Faroe Islands, etc.), both studies are based on sound scientific foundations. While the Seychelles Islands data indicate a 10 ppm maternal hair mercury level to be associated with no deleterious effects, the New Zealand study suggests that maternal hair mercury levels below 6 ppm are associated with brain function alterations in offspring (Kjellstrom et al., 1986; Davidson et al., 1998). A re-evaluation of these data resulted in a maternal hair mercury level that ranges from 7.4 - 10 ppm (Crump et al., 1998). The authors of the Faroe Islands studies indicate that early dysfunction in children is detectable at exposure levels resulting in maternal hair mercury levels below 10 ppm (Grandjean et al., 1997). Although only limited dose response data are available from this

study, the geometric average mercury maternal hair concentration for the cohort was provided as 4.3 ppm and control group formations were made with mothers who had lower exposures and mercury hair concentrations below 3.0 ppm (Grandjean et al., 1997, 1998).

Based on available data, a tolerable daily intake for the populations of greatest concern, women of child bearing age and infants, could be determined using mercury maternal hair or mercury cord blood exposure data. The pharmacokinetic variability would be less if mercury cord blood levels from the Faroe Islands cohort were used since empirical cord blood data would not require using mercury hair levels as the exposure metric to estimate maternal blood mercury which is itself an estimate of cord blood. Also, in a compartmentalized model that relates exposure to target organ dose, mercury cord blood, if strongly associated with mercury maternal blood, would be just one compartment removed from the target organ. At present, for the Faroe Islands study, only very limited dose response data are available and data on the relationship between maternal and cord blood levels for mercury are not yet available. Only the geometric average cord blood level of 22.9 µg/l has been provided, without any variance data.

Previous works have suggested that the average mercury cord blood levels are 20 – 30% higher than mercury maternal blood levels (Kuhnert et al., 1981). Dennis and Fehr (1975) analyzed paired maternal and cord blood samples for mercury from fish consuming women in northern Saskatchewan (n = 43) and non-fish consuming women living in southern Saskatchewan (n = 45). There was a positive association between mercury maternal and mercury cord blood levels in both regions with the correlation coefficients being 0.45 and 0.87 for the south and north, respectively. Only in the north though, was the mean mercury level significantly different (p< 0.01) between maternal and cord blood samples. The cord blood samples were higher for the north sample group with the slope of the regression being 1.3. Kuhnert and associates (1981) re-addressed this issue of maternal and cord blood mercury level differences using gas chromatography techniques, however, a limitation was that the sample size of the study group was small (n = 29). Methylmercury levels in both plasma and erythrocytes were investigated with 30% more methylmercury observed in fetal erythrocytes than in maternal, while plasma levels were not significantly different. "Total" mercury concentrations in blood were calculated and compared with other studies, with results from the various studies indicating that "total" mercury levels in fetal cord blood are 13% to 24% higher than those in maternal blood. Kuhnert and associates (1981) also suggested that fetal cord whole blood contained 32% more methylmercury than maternal whole blood which is similar to the increase observed between fetal and maternal red blood cells. Although the sample size is a limitation of this study, this work does suggest that the ratio of mercury cord blood levels to mercury maternal blood levels is greater than one.

Further indication that the ratio may not be equal can be found in data presented by Cernichiari and co-workers (1995) indicating that mercury infant blood levels are on average twice that of maternal blood. These data, however, may only be used to suggest that differences in mercury blood levels may exist since the mercury levels in fetal blood and infant blood can not be directly compared because they are not identical; for example, fetal hemoglobin, manufactured in the red blood cells of the fetus and infant compose 50% to 90% of the hemoglobin in the

newborn, however, it is mostly replaced by adult types (A_1 and A_2) by age six months (Fischbach, 1996).

By applying the ratio of mercury cord blood levels versus mercury maternal blood levels (1.3), suggested by data sets described above, to the available cord blood value of 22.9 µg/l, a maternal blood value of 17.6 µg/l is obtained. A daily intake of 0.36 µg/kg/day is then derived using the following algorithm relating mercury levels in maternal blood to a daily intake level (ATSDR,1997):

$$C = \frac{A_D * A_B * d * W}{b * V}$$

where,

C = mercury concentration in blood (mg/l),
A_D = percent of mercury intake in diet that is absorbed (95%),
A_B = percent of the absorbed amount that enters the blood (5%),
d = daily dietary intake (mg/kg),
b = elimination constant (0.014),
V = volume of blood in 60 kg woman (4.2 l), and
W = average body weight for women (60 kg).

Studies that have compared mercury maternal hair levels with mercury blood levels have produced various ratios ranging from 140 to 415 (Berglund et al., 1971; Birke et al., 1972; Davidson et al., 1995; Den Tonkelaar et al., 1974; Kershaw et al., 1980; Sherlock et al., 1982). Within this range of ratios which differ by approximately three, the most frequently used value has been 250. Blood samples were not obtained from the New Zealand cohort; however by applying this most frequently cited hair to blood ratio along with the 6 ppm maternal hair mercury value, a daily intake of 0.5 µg/kg/day is obtained. Also, by applying the hair to blood ratio of 250 to the Faroe Islands maternal hair levels of 4.3 and 10 ppm, a daily intake range of 0.35 to 0.8 µg/kg/day is obtained by using the algorithm relating mercury levels in blood to a daily intake level as described by ATSDR (1997). The geometric average maternal hair level of 4.3 ppm was used because the regression relationship between methylmercury exposure and adverse effects was derived from the entire cohort and the average value reflects that cohort (notwithstanding that the regression may be driven by values above or below the average value), while 10 ppm represents the cutoff value used in the bivariate categorical analyses which showed a significant difference for methylmercury effect above and below that value. Although only limited dose response data are available for the Faroe Islands population, the average maternal hair mercury level and the maternal hair mercury level of 10 ppm, below which early dysfunction is detectable, may provide a range that encompasses the intake level considered tolerable for that population. Also, this range encompasses the daily intake level obtained using cord blood data as well as the intake rate obtained from the New Zealand cohort results, even after re-evaluation of that data.

The use of these data, in light of the Seychelles Islands study results to derive a tolerable daily intake level, once again raises the issue of where these exposure levels are on the dose response curve. Confounders or other subtle factors presently not properly delineated may be responsible for the differences seen between populations that have similar mercury-hair concentrations and that are exposed in similar manners. Along with the possible population differences, some of the observed discrepancies may be due to the exposure metric, may it be cord blood or maternal hair, used in the different studies. Also, these exposure levels may be at or near the effect level such that other factors may determine if mercury exposure at these levels impacts brain function. Although the Seychelles Islands study did remove certain individuals from its cohorts based on very specific conditions, both the Faroe Islands and Seychelles Islands studies can be considered to be relatively inclusive in addressing the range of variability in dose-response which may be expected in populations such as those in the US. Both studies were specific to the most sensitive portion of the population (mother-infant pairs) and included those with relatively moderate rates of fish/whale consumption as well as those who would be considered to consume elevated quantities in the US. One limitation in interpretation of these studies, however, is that both studies implicitly assumed that adverse effects from methylmercury are associated with the average daily intake, and both mercury-hair concentration, and to some extent, mercury-blood concentration, reflect average intake. It is possible, however, that the adverse effects of methylmercury exposure are more directly related to the magnitude of peak exposure, as could result from one, or a few closely spaced meals of fish with high mercury concentration, rather than to average exposure level. If peak exposure were an important determinant in predicting adverse effects of methylmercury exposure, then exposure calculations based on average exposure metrics could result in significant exposure misclassification. This, in turn would reduce the predictive power of these studies. Unfortunately, neither study collected consumption frequency information by fish species which could have been useful in distinguishing the influence of average versus peak exposure.

Considering the totality of evidence from these studies with respect to effects observed at less than 10 ppm maternal hair mercury levels and the populations studied, determining the exact value that should be applied to address various uncertainties is demanding. The sensitive endpoints are impaired neurological development and, long-term and/or delayed sequelae. The studies used to derive a tolerable daily intake best address the former with long-term and/or delayed sequelae being effects that have only been observed and or studied in primates and in the catastrophic exposure to communities in Japan (Rice, 1992, 1996a; Harada, 1995). There is uncertainty associated with toxicodynamic variations within the populations, although given the cohort sizes and types, this variation may be small (Renwick, G., 1993; Dourson et al., 1996; ATSDR, 1997; Stern, 1997). The interindividual pharmacokinetic variability associated with determining a tolerable intake level based on hair mercury levels could be accounted for through the use of an uncertainty factor of three (Renwick, G., 1993; Dourson et al., 1996; ATSDR, 1997; Stern, 1997). In total, these variabilities and the lack of ability to address long-term and/or delayed sequelae warrant an additional reduction of one order of magnitude. Although this value may be too large, a present justification for a smaller value can not be garnered from available scientific evidence. As a result, the tolerable daily intake becomes the range of values from 0.035 to 0.08 µg/kg/day.

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